What is the relationship between consumption of plant n-3 fatty acid and risk of cardiovascular disease?

Conclusion

Alpha-linolenic acid (ALA) intake of 0.6-1.2 percent of total calories will meet current recommendations and may lower cardiovascular disease (CVD) risk, but new evidence is insufficient to warrant greater intake beyond this level. Limited, but supportive evidence suggests that higher intake of n-3 from plant sources may reduce mortality among persons with existing CVD.

Grade: Limited

Overall strength of the available supporting evidence: Strong; Moderate; Limited; Expert Opinion Only; Grade not assignable For additional information regarding how to interpret grades, click here

Evidence Summary Overview

The Nutrition Evidence Library (NEL) conducted an evidence review to determine the relationship between consuming plant-derived omega-3 polunsaturated fatty acids (n-3 PUFA) and the risk of cardiovascular disease (CVD) events. This review relied upon an evidence-based review conducted by the American Dietetic Association (ADA) on the relationship between n-3 fatty acids (n-3 FAs) and CVD, covering the literature from 2004 to 2007 (ADA, 2008). Overall, five studies were reviewed by ADA that addressed this question. These included two methodologically strong case-control studies (Lemaitre, 2003; Rastogi, 2004), and three prospective cohort studies (two were methodologically strong [Albert, 2005; Mozaffarian, 2005] and one was methodologically neutral [Folsom and Demissie, 2005]). In addition, the NEL reviewed three studies since 2008, including one methodologically strong case-control study conducted in the US (Lemaitre, 2009), one methodologically strong prospective cohort study covering 2,682 men in Finland (Virtanen, 2009), and one methodologically strong systematic review of 14 randomized controlled trials (RCTs), 25 prospective cohort studies and seven case-control studies (Wang, 2006).

Two studies of persons with CVD were part of the 2008 ADA review. One methodologically neutral RCT (Baylin, 2003) and one methodologically neutral case-control study (De Lorgeril, 1999) found a diet high in plant-derived n-3 FAs protective against recurrence of myocardial infarction (MI).

Evidence Summary Paragraphs

Systematic reviews/Meta-analyses

Wang et al, 2006 (positive quality). This was a systematic review that investigated the effects of n-3 FAs, consumed as fish or fish oils rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) or as alpha-linolenic acid (ALA), on CVD outcomes. Studies that were of less than or equal to one year in duration and that reported estimates of fish or n-3 FA intakes and CVD outcomes were included. Fourteen RCTs (11 fish oil supplement trials, five diet or diet advice trials) and one prospective cohort study addressed secondary prevention. One RCT assessing ALA supplementation, 25 prospective cohort studies and seven case-control studies reported on the association of n-3 FAs with primary prevention of CVD. Most cohort studies reported that fish consumption was associated with lower rates of all-cause mortality and adverse cardiac outcomes. Three studies assessed the effects of increased intakes of ALA, which were estimated to be between 1.8 and 6.3 g per day (Singh RB et al, 2002 and Bemelmans et al, 2002). No firm conclusions regarding the effects of either ALA or the marine n-3 FA could are reached from these trials. Two of the ALA dietary trials reported significant reductions or trends toward lower rates of all-cause mortality, cardiac and sudden death, or non-fatal MI (Singh RB et al, 2002 and de Lorgeril et al, 1999), whereas the third trial reported a non-significant (NS) increase in the risk of all-cause mortality (Bemelmans et al, 2002), which was very low in both groups. Evidence suggests that increased consumption of n-3 FAs from fish or fish-oil supplements, but not of ALA, reduces the rates of all-cause mortality, cardiac and sudden death.

Primary Articles

Albert et al, 2005 (positive quality) cohort study (N=76,763 females, 50.8±7.1 years of age), found in an age-adjusted

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analysis, a trend toward a lower risk of sudden cardiac death with greater ALA intake (ALA source not specified). This relationship became significant (P=0.02) in the fourth quintile of intake, a median absolute intake of 1.16g per day. For every 0.1% increase in energy intake from ALA, the associated hazard ratio was 0.88 (95% CI: 0.80 to 0.98). Women in the two highest quintiles of ALA intake had a 38% to 40% lower sudden cardiac death risk. Intake of ALA was NS related to other non-sudden fatal coronary heart disease (CHD) events or to non-fatal MI.

Baylin et al, 2003 (neutral quality) case-control study, found an inverse relationship (P<0.0001) in 482 cases and controls, between adipose tissue ALA and risk of non-fatal acute MI. The greatest protection was found in those individuals who also had low total trans fatty acids (TFA) in adipose tissue (P<0.05). Subjects in the top quintiles of adipose tissue ALA (0.72% of fatty acids) had a lower risk of MI than those in the lowest quintile (0.35% of fatty acids) (P<0.0001). The difference in adipose tissue ALA corresponds to approximately 0.3g per day of dietary intake.

De Lorgeril et al, 1999 (neutral quality) RCT, reported a decreased rate of cardiac death and non-fatal MI in 423 subjects following a Mediterranean diet vs. a Western diet (1.24 vs. 4.07 per hundred patients per year) for 46 months. The experimental group had a significantly lower intake of total lipids (P=0.02), saturated fats (P=0.0001) and increased intake of oleic, linoleic and ALA fatty acids (P=0.0001). The plasma concentration of 18:3 (ω-3) and 22:6 (ω-3) tended to be inversely associated with recurrence of MI (P=0.11 and P=0.16, respectively).

Folsom and Demissie, 2005 (neutral quality), prospective cohort study, assessed the effect of fish or marine n-3 FA intake on CVD and CHD mortality over a 10-year period in 41,836 postmenopausal women aged 55-69 years, initially free of heart disease and cancer (4,653 deaths over 442,965 person-years). A food frequency questionnaire (FFQ) was used to determine if intake may decrease risk of total and CHD death. Among women initially free of heart disease and cancer there was an inverse age- and energy-adjusted association between total mortality and fish intake, with a relative risk (RR) of 0.82 (95% CI: 0.74, 0.91) for the highest vs. lowest quintile. Age- and energy-adjusted associations also were inverse (P for trend<0.05), although not entirely monotonic, for cardiovascular, CHD and cancer mortality. Adjustment for multiple other risk factors attenuated all associations to statisticallyNS levels. Estimated marine n-3 FA intake also was not associated with total or cause-specific mortality. In comparison, plant-derived ALA was inversely associated with mortality after multivariable adjustment.

Lemaitre et al, 2009 (positive quality), case-control study in which the researchers investigated the association of red blood cell RBC) membrane ALA with sudden cardiac arrest risk in 265 cases, aged 25 to 74 years, who were out-of-hospital sudden cardiac arrest patients attended by paramedics and were free of prior clinically diagnosed heart disease. The study was conducted in the US (Seattle). Controls (N=415) were randomly identified from the community, and matched to cases by age, sex and calendar year. Blood was obtained at the time of cardiac arrest (cases) or at the time of an interview (controls) and analysis of the samples showed that higher membrane ALA acid was associated with a higher risk of sudden cardiac arrest. Alpha-linolenic acid levels were positively associated with RBC membrane levels of linoleic acid (r=0.39), trans-18:2 (r=0.22) and eicosapentaenoic acid (EPA) (r=0.16), but not with docosahexaenoic acid (DHA) (r=0.04). After adjustment for matching factors, smoking, diabetes, hypertension (HTN), education, physical activity, weight, height and total fat intake, the odds ratios (OR) corresponding to increasing quartiles of ALA were 1.7 (95% CI, 1.0-3.0), 1.9 (95% CI, 1.1-3.3) and 2.5 (95% CI, 1.3-4.8) compared with the lowest quartile. An increase in ALA corresponding to one standard deviation (SD) was associated with 32% higher risk of sudden cardiac arrest (OR=1.32, 95% CI: 1.07-1.63) after adjustment for confounding variables. The association was independent of red blood cell levels of long-chain n-3 FAs, TFAs, and linoleic acid. Authors concluded that higher membrane levels of ALA are associated with higher risk of sudden cardiac arrest.

Lemaitre et al, 2003 (positive quality), case-control study (N=179 pairs) nested in the Cardiovascular Health Study cohort, found free-living older adults (over 65 years of age), after adjustment for risk factors, a higher concentration of combined plasma DHA and EPA was associated with a lower risk of fatal ischemic heart disease (IHD). Based on data from 54 cases of fatal IHD, 125 cases of non-fatal MI and 179 matched controls, for a one-SD increase in plasma phospholipids DHA and EPA, there was an associated 70% lower risk of fatal IHD (OR: 0.30; 95% CI: 0.12, 0.76; P=0.01) and for a one-SD increase in ALA, there was an associated 50% lower risk of fatal IHD (OR: 0.48; 95% CI: 0.24, 0.96; P=0.04). The first controlled for coronary risk factors, updated prior report of CVD, alcohol intake, aspirin, vitamin supplements and postmenopausal hormone use. The second included the covariates in model one and additionally controlled for intake of other fatty acids that resulted in a change of more than 10% in the parameter estimate for ALA intake.

Mozaffarian et al 2005 (positive quality) 14-year prospective cohort study, examined the interplay between intermediate and long chain n-3 FA and n-6 FA intake on the incidence of CHD in 45,722 male health professionals. Dietary n-3 FA and n-6 FA intake were assessed by administration of a self-administered validated FFQ at multiple time-points and development of CHD assessed by a biennial health history questionnaire. Relative risk of non-fatal MI

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was lower in those with high intakes of ALA (RR=0.58; 95% CI 0.23 to 0.75). The effect of ALA on total CHD and non-fatal MI occurred mostly in men with low intakes of EPA plus DHA. Long-chain and intermediate-chain n-3 FA intakes were associated with lower CHD risk, without modification by n-6 FA intake when adjusted for age; body mass index (BMI); smoking; physical activity; history of diabetes, HTN or hypercholesterolemia; aspirin use; alcohol use; and intake of protein, saturated fat (SFA) dietary fiber, monounsaturated fat (MUFA), trans fatty acids (TFA), total calories and ALA. High intake of EPA plus DHA (more than 250mg per day or equivalent to one or two fish meals per week) compared to low intake (less than 250mg per day) was associated with a 35% lower risk of sudden death (RR=0.65; 95% CI; 0.47 to 0.88). High intake of EPA plus DHA was associated with reduced sudden death regardless of ALA level.

Rastogi et al, 2004 (positive quality), case-control study (N=350 cases and 700 controls), found a lower relative risk of IHD in those using mustard oil, which is rich in ALA, for cooking (RR=0.49; 95% CI: 0.24, 0.99) vs. those who used sunflower oil. The risk was further reduced when the mustard oil was used for frying (RR=0.29; 95% CI: 0.13, 0.64). Individuals using vanaspati, a hydrogenated vegetable oil, were at a slightly, but not significantly, higher risk of IHD than those not using it (RR: 1.81; 95% CI: 0.99, 3.31).

Virtanen et al 2009, positive quality prospective population-based cohort study, examined the relationship between serum concentrations of long-chain n-3 PUFAs, EPA, docosapentaenoic acid (DPA) and DHA, which also serve as a marker of fish or fish oil consumption, and risk of atrial fibrillation (AF) in middle-aged or older men, 42-60 years old and free of AF at baseline (1984-1989) in Eastern Finland. During 17.7 years of follow-up, 240 men from the total cohort of 2,174 men experienced an AF event that required hospitalization. Men in the highest quartile of serum EPA+DPA+DHA had a 35% lower risk of AF compared with men in the lowest quartile. Of the individual fatty acids, only serum DHA was associated with the risk, with a 38% lower risk in the highest quartile. No association with the risk was found with serum intermediate chain-length n-3 PUFA, ALA, not even when the serum EPA+DPA+DHA concentration was low. Authors conclude that long-chain n-3 PUFAs, and especially DHA, may be effective in reducing the risk of AF.

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Author, Year, Study Design, Class, Rating	Study Population/Location	Intervention Protocol/Exposure levels	Significant Results	Limitations
Albert et al 2005 Study Design: Prospective Cohort Study Class: B Rating:	N=76,763 women. Age: 50 years (SD 7.1). Participating in Nurses' Health Study (97,423). Completed the baseline FFQ. Location: United States.	ALA intake SCD. Five semi-quantitative FFQ between 1984 and 1998. Follow-up questionnaires for exposure information and new medical illnesses.	ALA-predominant n-3 fatty acid consumed: Mean absolute intake: 0.66g per day in the lowest and 1.39g per day in the highest quintile. Greater ALA intake was associated with a trend toward a lower risk of sudden cardiac death: • For every 0.1% ↑ in energy intake from ALA, the associated HR=0.88. • Women in the two highest quintiles of ALA intake had a 38-40% ↓ SCD risk. • ALA intake related to other non-sudden fatal CHD events or to	As do other similar studies, this cannot prove causality, since association between ALA consumption and SCD could, at least in part, have been caused by residual confounders Information on coronary risk and diet was ascertained by self-reporting, potentially leading to some misclassification.

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			non-fatal MI.	
Baylin A, Kabagambe EK, et al 2003 (Circulation) Study Design: Case control. Class: C Rating:	482 case patients with first nonfatal acute MI and 482 matched controls. Location: Costa Rica.	Subcutaneous adipose tissue biopsy to assess ALA content. FFQ (ALA content of diet not assessed).	Cases had lower adipose tissue ALA levels (P=<0.001). An inverse relationship between adipose tissue ALA and the risk of non-fatal acute MI. Subjects in the top quintiles of adipose tissue ALA (0.72%) had a ↓ risk of MI than those in the lowest quintile (0.35%). The difference between the two groups corresponded to ~0.3g per day of intake.	Biomarkers are prone to misclassification because of laboratory error.
De Lorgeril M, Salen P, et.al. 1999 Study Design: Randomized controlled trial. Class: A Rating:	N=423 (204 controls and 219 experimental). Survivors of MI. Age: <70 years. Location: France.	Mediterranean-type diet vs. prudent diet. Investigator designed mediterranean style diet vs. prudent diet from private physician.	All-cause and cardiovascular mortality (P=0.01) and the combination of recurrent MI and cardiac death (P=0.0001) were ↓ with the Mediterranean diet The experimental group had a significantly ↓ intake of total lipids (P=0.02), SFA (P=0.0001) and ↑ intake of oleic, linoleic and ALA fatty acids (P=0.0001). Plasma concentration of 18:3 (ω-3) and 22:6(ω-3) tended to be inversely associated with recurrence of MI (P=0.11 and 0.16, respectively).	The Lyon Diet Heart Study had been previously published; not all of the details of the study were included in this paper.
Folsom and Demissie, 2004 Study Design: Cohort study. Class: B Rating:	N=41,836 post menopausal women without initial history of heart disease from Iowa. Locatin: United States.	Fish or marine n-3 FA intake and cause of death (CVD or CHD). Baseline dietary intake assessed in 1986 using a FFQ with four fish and seafood questions. Mean respective intakes of EPA, DHA and total marine n-3 FAs were	Plant-derived ALA was inversely associated with mortality after multivariable adjustment. No independent association of fish intake with CVD, CHD or stroke mortality.	Self-reported a prior history of MI, angina or other heart disease. Causes of death not verified. Single self-reported of

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		53mg, 135mg and 188mg per day. The mean intake of ALA was 1.09g per day.		usual fish intake may result in errors of recall.
Lemaitre et al 2009 Study Design: Case-Control Study Class: C Rating:	N=265 married residents of King. N=415 controls randomly identified from and matched to cases by age, sex and calendar year. Age: 25-74 years. Location: United States.	**Serum EPA+DHA+DPA+ALA and SCA** No intervention. Out-of-hospital SCA subjects in Seattle Washington, between 1988 and 2005. SCAis a sudden pulse-less condition in the absence of evidence of a non-cardiac cause of cardiac arrest. Identified from EM incident reports, incident reports, death certificates, medical examiner reports, and autopsy reports to exclude patients with cardiac arrest due to a non-cardiac cause. Administered a FFQ to 81 controls. For each food item, controls were asked to estimate usual serving size and frequency of consumption of 120 line items during the prior month Nutrient intake estimated from the questionnaire database that is derived from the University of Minnesota Nutrition Coding Center nutrient database.	Subset of control: Average total fat intake=36.0% of total energy (7.8% energy from PUFA); and mean dietary intake of ALA was 1.9g per day. RBC membrane ALA levels modestly related to the estimate of ALA intake adjusted for total caloric intake (r=0.21, P=0.06). The RBC membrane levels of ALA were not related to total caloric intake (r=0.04) and to SFA intake (r= -0.01. Mean RBC ALA levels ↑ in Cases than Controls. ALA positively associated with RBC membrane levels of LA (r=0.39), levels of trans-18:2 (r=0.22), and levels of EPA (r=0.16), but not with levels of DHA (r=0.04). RBC membrane levels of ALA associated with ↑ risk of SCA. An ↑ in ALA corresponding to one STD associated with 32% ↑ risk of SCA (OR, 1.32; 95% CI, 1.07-1.63).	Measured dietary ALA in a small subset of controls, and could not contrast the associations of diet and membrane levels. ALA with SCA within this study population. Could result in residual confounding such incompletely adjusted for SFA intake. Use of surrogate respondents inevitably introduced some misclassification in assessment of potential confounders. Participation rate in the control=60%, and the OR associated with higher levels of ALA could be overestimated if controls who declined participation in the study ate more ALA-containing foods than the controls who participated.

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Lemaitre RN, King IB et al, 2003 Study Design: Prospective nested case-control Class: C Rating:	54 cases of fatal IHD, 125 cases of non-fatal MI and 179 matched controls of free living adults. Age: >65 years.	**Serum EPA+DHA+ALA and IHD** No intervention. Plasma phospholipids concentrations of DHA, EPA and ALA taken two years before the event were used as a biomarker for intake. Fish oil supplement users excluded from the study.	Higher concentration of combined DHA and EPA was associated with a ↓ risk of fatal IHD (OR: 0.30 (95% CI: 0.12, 0.76; P=0.01). No association with non-fatal MI.	None.
Mozaffarian D, Ascherio A et al, 2005 Study Design: Prospective 14-year follow-up study of dietary n-3 and n-6 intake assessed by administration of a self-administered validated FFQ at multiple time points and development of CHD assessed by biennial health history questionnaire. Class: B Rating:	N=45,722 male health professionals from the US. Prospective 14-year follow-up study of dietary n-3 and n-6 intake assessed by administration of a self-questionnaire. Location: United States.	Dietary n-3 and n-6 intake: Assessed by a self-administered validated FFQ at baseline and every four years. Development of CHD assessed by biennial health history questionnaire.	High intake of EPA+DHA intake (>100mg per day) compared to low intake (<100mg per day): • Associated with a 35% ↓risk of sudden death (HR=0.65; 95% CI=0.47 to 0.88) • High intake of EPA+DHA associated with ↓ sudden death, regardless of ALA level.	Relatively small number of incident fatal IHD events and the indirect assessment of dietary PUFAs.
Rastogi, Reddy et al, 2004 Study Design: Case-control. Class: C Rating:	N=350 cases of first MI. N=700 controls (12% female) eastern Indian individuals. Location: India.	**Mustard oil (high in ALA) vs. Sunflower oil and IHD** Food Frequency and Activity questionnaires.	Suggestive trend of ↓ risk with fish intake (RR=0.69; 95% CI: 0.46, 1.03), but not with vegetarianism Use for Cooking: Mustard oil (high ALA): Compared to sunflower oil - RR=0.49 (95% CI: 0.24, 0.99) for IHD. Use for Frying: Mustard oil=RR of 0.29 (95% CI:	Potential sources study includes the selection of controls and a differential recall among cases and controls. No companion nutrient database was available for FFQ; hence total

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			0.13, 0.64) in multivariate analysis. Adding vanaspati (hydrogenated vegetable oil) to foods slightly, but NS ↑ risk of IHD over those who did not (RR=1.81; 95% CI: 0.99, 3.31).	energy intake could not be computed. Differential recall of dietary intake from different sites could be a potential concern. Study controls were more educated.
Virtanen et al 2008 Study Design: Prospective Cohort Study Class: B Rating:	Health professionals aged 40-75 years. Health Professionals Follow-up Study. 18 years of follow-up. Location: United States.	**Fish and n-3 fatty acid intake and total major chronic disease.** Multiple validated FFQ over time used to compute cumulative averages of dietary intake. Fish intake based on 131-item food FFQ. Intake and amounts of four different seafood items: Canned tuna fish, dark meat fish (mackerel, salmon, sardines, bluefish and swordfish), other fish (not specified) and shrimp, lobster or scallops as a main dish **Fish intake in categories:** • One to three servings per month, one serving per week • Two to four servings per week, >five servings per week.	During 18 years of follow-up, 9,715 (24.1%) major chronic disease events occurred: • 3,639 CVD events • 4,690 cancers • 1,386 deaths other causes. Baseline, mean (±SD) EPA+DHA intake was 0.3±0.2g per day and fish intake per day, was 0.3±0.3g per day compared to men with ↓ fish intake: Men with ↑ fish intake more likely to be physically active, have hypercholesterolemia and HTN, use aspirin and multivitamin supplements, drink more alcohol and smoke. Men with higher fish intake consumption: Have ↑ intakes of energy, protein, EPA+DHA, PUFA, fiber, fruit and vegetables and ↓ intakes of SFA, MUFA and TFA. **Age-adjusted analyses:** Fish intake inversely associated with risk of major chronic disease (P for trend=0.02). **Multivariable adjustment:** Neither fish nor dietary n-3 FA intake was significantly associated with risk of total major chronic	Databases used may not reflect rapid changes in the use of different types of vegetable oils in the food supply. Did not evaluate the potential effects of fish or EPA+DHA intake on other specific disease outcomes, such as heart failure, atrial fibrillation, that may be improved by fish intake.

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			disease. Compared with fish consumption of Fish intake more than five servings per week not associated with lower risk. Higher or lower n-6 FA intake: NS modification of the results (P for interaction >0.10).	
Wang et al 2006 Study Design: Systematic Review Class: M Rating: 	N=46 articles identified: • 14 RCTs • 25 prospective cohort • Seven case-control. Secondary prevention trials (11 RCTs): • Total subjects: N=19,403 • One prospective cohort study: Total N=415. **Primary prevention trials:** • One RCT • 25 cohort (N>340,000) • Seven case-control. Three estimated ALA intakes. Studies that were of ≥ one year in duration. Location: United States, Europe, China, Japan.	**Fish, Fish oil and ALA intake and CVD** Comprehensive search 1966 to July 2005. n-3 FAs, consumed as fish or fish oils rich in EPA and DHA or as ALA, on CVD outcomes. **Secondary prevention studies:** • Investigated 14 RCTs (11 fish oil supplement trials, five diet or diet advice trials) • One prospective cohort study. **Primary-prevention studies:** • 11 RCT assessing ALA supplements • 25 prospective cohort studies and seven case-control studies reported on the association of n-3 FAs with CVD.	After controlling for age, randomization to aspirin and β-carotene and coronary risk factors: Dietary fish intake was associated with a ↓ risk of sudden death, with an apparent threshold effect at a consumption level of one fish meal per week. (P for trend=0.03).	No meta-analysis conducted.

Research Design and Implementation Rating Summary
For a summary of the Research Design and Implementation Rating results, click here.

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Worksheets

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